Proton- Radiotherapy:

Future of Medical Indications and Treatment Concepts

Eugen B. Hug and Ralf A. Schneider
The „emerging“ role of Proton Radiotherapy in the framework of modern Photon-RT

- 2000:

  - Exclusive role in rare diseases
  - Small role in frequent malignancies
  - Protons

Photons
The „emerging“ role of Proton Radiotherapy in the framework of modern Photon-RT

Emerging role in frequent malignancies

Exclusive role in rare diseases
The future role of Proton Radiotherapy in the framework of modern Photon-RT

*The 2 (historic) legs of Proton Radiotherapy*

- High-Dose Target coverage
- Reduction of low-moderate dose volume
The future role of Proton Radiotherapy in the framework of modern Photon-RT

a) High Doses to Targets:

- Future role compared to other modalities needs to be defined. Many areas are already or will be well covered by SBRT, RS, i.e. stereotactic Linacs, Cyberknife, Tomotherapy.
- The exclusive high-dose advantage of protons over photons – present until mid-90’s - has essentially vanished.
- General statements about superiority of protons to cover the target with high doses over photons no longer hold up.
The future role of Proton Radiotherapy in the framework of modern Photon-RT

a) High Doses to Targets:

- Dependent on site and sub-groups of diseases, advantages still persist – however, it is up to the proton users to carefully uncover and crystallize those advantages site-by-site, disease-by-disease.
- Comparisons with Cyberknife, Tomotherapy etc. will become increasingly important
The future role of Proton Radiotherapy in the framework of modern Photon-RT

The need for HYPOTHESIS-based Proton Therapy:

- protons have in important areas lost the leadership in clinically innovative treatment designs
- The last 10 years have been significant for lack of innovative approaches
- We are now paying the price and have to catch up.
Proton Radiotherapy in the framework of modern Photon-RT

- The last 10 years have been significant for lack of innovative approaches

Example: Prostate-Ca

- For 10 years no new trial design
- No hypofractionation (only now….)
- No biologic targeting-based approach
- No dose escalation beyond photons

Anthony Zietman:

- „The Titanic and the Iceberg“: Prostate proton therapy and health care economics, JCO 25(24):3565
- I’m fascinated and horrified by the way it’s developing,” A. Zietman {on protons for prostate Ca} “This is the dark side of American medicine.” (The New York Times, Dec. 2007)
A TREATMENT PLANNING COMPARISON OF COMBINED PHOTON–PROTON BEAMS VERSUS PROTON BEAMS–ONLY FOR THE TREATMENT OF SKULL BASE TUMORS

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IJROBP 69(3):944, 2007

• 67 Gy total dose, 45 Gy Photons, 22 CGE Protons
• 10 patients with skull base tumors planned
• Results:
  • Mean GTV doses not signif. different,
  • minimum GTV doses higher with protons only,
  • Target dose homogeneity better with protons only
  • CI80% for GTV and CTV higher with protons (95% similar)
Cumulative dose–volume histograms for brain stem, chiasm, eyes, optic nerves, and internal ears for 10 patients.

„Use of protons lead to significant reduction of Normal Tissue and OAR irradiation in the intermediate to low dose range (< 80% isodose line)“
Protons as Boost only in combination with photons

Feuvret et al., IJROBP 69(3):944, 2007

Authors‘ conclusions:

- Combination treatment permits similar doses to be delivered to the targets, i.e. combination of photons/protons is a feasible alternative.
- „Protons only“ are recommended in children
Protons as **Boost** only in combination with photons

Feuvret et al., IJROBP 69(3):944, 2007

„**PRO“** Boost:

Practical approach if primary endpoint is delivery of high target dose only

Practical approach if primary concern is patient throughput (high demand, low capacity), i.e. making protons available to maximum number of patients (example: national centers)

„**CONTRA“** Boost

- article demonstrates persistent assumption that even doses up to 50 Gy „do not matter“ in adult patients, i.e. have no detrimental effects.
- Benefits of reduction of Integral dose by protons will not be utilized.
Conventional Wisdom:

„Proton Therapy reduces the volume of normal tissue receiving low-dose radiation „

and

„The low-dose volume is largely irrelevant for adult patients“ (a necessary assumption for advocates of Tomotherapy, SBRT, etc. over Protons)
Conventional Wisdom (i.e. my personal interpretation):

Definition / general agreement / common understanding on dose-terminology* of:

„low“
moderate“
„therapeutic range“
„high-dose“

* = for use in radiooncology, not general public
Conventional Wisdom (i.e. my personal interpretation)*:

„low“ dose range
1 Gy ---- 10/15 Gy

„moderate“ dose range
15/20 --- 35/45 Gy

„high“ dose range
60/65 Gy and up

50/55 Gy and up

„therapeutic“ dose range
(most solid tumors)

ICRU: < 5% isodose (report in progress)

BEIR IV Committee: < 0.1 Gy

* = for use in radiooncology, not general public
Planning-Comparison: **Tomotherapy versus IMPT**

for high-risk Prostate CA –

RT to prostate, seminal vesicles and pelvic LN‘s

_Lamberto Widesott, Claudio Fiorino, Ralf Schneider, Tony Lomax_
Tomotherapy

IMPT

78 Gy

15 Gy
Tomotherapy

IMPT

78 Gy

15 Gy
IMPT 3 fields vs IMPT 2 fields and virtual blocks

Widesott, Schneider et al., PSI 2009
Conformity Index

Conformity index 1 = \[
\frac{\text{Volume of body receiving 90% of 74.2 Gy}}{\text{Volume (prostate + 1/3 vesicles)}} = \frac{1.70}{1.35}
\]

Conformity index 2 = \[
\frac{\text{Volume of body receiving 90% of 65.5 Gy}}{\text{Volume (prostate + vesicles)}} = \frac{2.09}{1.63}
\]

Conformity index 3 = \[
\frac{\text{Volume of body receiving 90% of 51.8 Gy}}{\text{Volume (total PTV)}} = \frac{1.80}{1.40}
\]
Tomotherapy vs IMPT 3 fields

- Bladder_Tomo
- Rectum_Tomo
- Bulb_Tomo
- Bladder_Proton
- Rectum_Proton
- Bulb_Proton

Dose [Gy]
Tomotherapy vs IMPT 3 fields

- Low-dose
- Tomo
- Moderate dose

Dose [Gy]

- Bladder_Tomo
- Rectum_Tomo
- Bulb_Tomo
- Bladder_Proton
- Rectum_Proton
- Bulb_Proton
Volume Comparison of Proton Therapy and Intensity-Modulated Radiotherapy for Prostate Cancer

Vargas et al, IJROBP 2008, 70(3):744
Volume Comparison of Proton Therapy and Intensity-Modulated Radiotherapy for Prostate Cancer


Vargas et al, IJROBP 2008, 70(3):744
Conventional Wisdom:

"Proton Therapy reduces the volume of normal tissue receiving low-dose radiation."

Planning comparisons demonstrate a reduction of the integral dose by proton therapy most pronounced in the low dose range, but extending well into the moderate and even therapeutic dose range.
Proton Radiation Therapy:

- *It has been proven beyond any reasonable doubt, that Proton Radiotherapy decreases the Integral Dose, thus decreases the amount of normal Tissues Irradiated compared to any Photon modality*
- *This advantage will persist in the foreseeable future.*
Proton Radiation Therapy: The low-moderate dose volume

- the Pediatric Oncology Community (USA, Europe) has already embraced the benefits of decreased integral dose by permitting protons in its protocols (COG).

- DE FACTO: in Pediatric Radiation Oncology a better isodose distribution by protons has been accepted as surrogate for clinical outcomes data.

- It is paramount to transfer this approach to the adult patient population.

- QoL Studies in the adult patient would solidify acceptance of protons.
The Focus of future Indications for Proton Therapy:

**LARGE Tumor / Target Size:**

Caveat: Increasingly effective Chemo-Tx replaces / reduces role of RT for microscopic disease

Examples:

- **Medulloblastoma** (from posterior fossa to reduced field, from 36 Gy to 18 Gy)

- **Hodgkin’s Disease** (from Inverted Y and Mantle to involved field, residual disease only, from 40 Gy to < 20 Gy to no RT)

- **Acute Leukemias** (prophylactic whole brain obsolete)
The Focus of future Indications for Proton Therapy: LARGE Target sizes

However……

Each step of dose reduction in pediatric tumors takes about 5-8 years (medullo, Hodgkin’s etc.)

Important large-field indications for solid tumors, where mod.- low dose reduction will continue to be of interest (examples):

Central Thorax (mediastinum)
Mesothelioma
Abdominal and Pelvic LN coverage.
The Focus of future Indications for Proton Therapy:

**SMALL**Tumor / Target Size:

Examples:
- Integrated boost
- Proton Radiosurgery (larger AVM‘s)
- multiple clinical indications (retinoblastoma)

……and many others
A New Approach to Proton-Therapy for Chordomas: Dose escalation via Integrated Boost

Concept: maintain same OAR constraints.

Integrated boost from 74 CGE (present GTV dose) to 88 CGE, accepting dose inhomogeneity (QUASI-radiosurgery)

(Caveat: Functioning tissue/nerves within GTV)
A New Approach to Proton-Therapy for Chordomas: Dose escalation via Integrated Boost
A New Approach to Proton-Therapy for Chordomas:
Dose escalation via Integrated Boost
The Focus of future Indications for Proton Therapy:

- **NEW** Indications and Applications

A static „list of indications“ is a desired goal of health care politicians and insurance companies (mainly in Europe) but has no medical meaning.

Applications for proton-radiotherapy will undergo rapid changes with increasing availability of protons in larger academic centers and evolving data – regardless if based on Level-1 evidence or not.

For many entities protons will be applied large scale for the first time within the coming years.
Some more predictions………..

Protons will be applied largely to replace photons – counting on the potential of reduced side effects.

Few Centers will have the resources to contribute academically to define the true benefits, potential, and limitations of protons.

Few centers will dare to explore the boundaries of protons.

Protons are a great tool for hypofractionation and inside-the-target dose painting (SIB, selective dose escalation within GTV) – they should be explored accordingly.

It would be desirable to define systematically the disease-specific subgroups of patients, that benefit most – rather than claim benefit for all.
Patient / Disease Selection Policy at PSI:

Example: Breast CA
Photon-Proton Planning Comparison of VARIOUS Irradiation Scenarios in the treatment of Breast Cancer:

A Collaboration between PSI (C. Ares, T. Lomax) and KS-Aarau (S. Bodis)

Scenarios: 10 patients. Tx-planning comparisons: 3D photons, IMRT, Protons

• 1 - Partial Breast Irradiation

• 2 - Whole Breast Irradiation +/- nodal areas

• 3 - Complex Breast and Nodal Irradiation including Internal Mammary LN, Axillary LN and Supraclavicular LN

Ares et a. IJROBP Epub
Collaboration PSI (C. Ares, T. Lomax) and KS-Aarau (S. Bodis)
Photon-Proton Planning Comparison of VARIOUS Irradiation Scenarios in the treatment of Breast Cancer:

A Collaboration between PSI (C. Ares, T. Lomax) and KS-Aarau (S. Bodis)

Results:

• Complex Breast and Nodal Irradiation including Internal Mammary LN, Axillary LN and Supraclavicular LN: Likely highest clinical advantage for protons for a scenario that is in general „unattractive“ and difficult for photons.
Proton Radiation Therapy: Future developments

• Radiobiology:
  • Potential to uncover proton-specific radiobiologic events, that would permit proton-specific combined multimodality treatment concepts
  • a potential, future 3rd leg of proton therapy?
The potential of uniquely combining particle therapy with systemic biologic agents / chemotherapy is presently untapped. – Basic radiobiology needs to be fostered to uncover potentially particle-exclusive cellular interactions within the oncogenic signal pathway or molecular interaction in general.

An exclusive interaction mechanisms for particles compared to photons will create opportunities for hypothesis-based, innovative multimodality treatment concepts.
Biologic imaging of clonogenic active tumor components within the anatomic tumor volume requires selective dose targeting within the tumor. Dose escalation of entire anatomic tumor volumes will reach its limitations due to surrounding normal tissue dose constraints.

Next-generation spot scanning should facilitate selective dose increase, i.e., intratumoral dose boosting. The capabilities of photon technology will likely parallel this process. The outcome is not yet decided.
Integration of Proton-Radiotherapy in national/international Cooperative Groups

- **Advantages:**
  - Patient participation in multimodality protocols increases standards of care.
  - Pts. / Parents do not have to choose between Study participation and Proton-RT.
  - Increasing acceptance by oncology community.
  - Endpoint data analyzed by outside institution permits objective data, permits (non-randomized) comparison with photons.
  - Local control and survival can be compared as part of subgroup-analysis with photons.
Integration of Proton-Radiotherapy in national/international Cooperative Groups

- **Present Disadvantages:**
  - Replacing photons with protons in a study protocol will not alter the expected tumor control and survival: Same dose and volume prescription.
  - Presently no proton-specific protocol defined that explores exclusively benefits of Protons. Example: Dose Escalation for difficult to treat tumors with presently poor local control.
Integration of Proton-Radiotherapy in national/international Cooperative Groups

Note: at present, large cooperative oncology groups (RTOG, ESTRO etc) do not provide (or have not been explored sufficiently- COG?) a platform to conduct proton specific trials.

PTCOG is a very valuable international group, but has not and likely will never have the logistical infrastructure to conduct clinical trials.
Proton-Radiotherapy at PSI: Quo Vadis?
CPT/ PSI
Beam Time Availability for Patient Treatments:

• CPT at PSI:
  • Unique Situation of
    – Product Developer (R&D)
    – Product Builder/Producer
      – Product Enduser

  – ........................................In ONE facility
"BEAM TIME" – A SCARCE RESOURCE

COMPETING TASKS:

- PATIENT TREATMENT
- SERVICE / MAINTENANCE (ROUTINE)
- UPDATES: -ACCELERATOR -BEAM LINE -CONTROL SYSTEMS
- R&D
- MED-PHYSICS TREATMENT PREPARATION
- COMMISSIONING OPTIS2
- INSTALLATION GANTRY 2
- MED-PHYSICS TREATMENT PREPARATION
- COMMISSIONING OPTIS2
- INSTALLATION GANTRY 2
### CPT: Capacity allocation on Gantry-1 2008

(changing priorities with increasing patient numbers)

<table>
<thead>
<tr>
<th>1/3</th>
<th>PEDIATRIC TUMOURS</th>
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<tr>
<td>1/3</td>
<td>CHORDOMAS / CHONDROSARCOMA of Skull Base and Axial Skeleton</td>
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| 1/3 | • SKULL BASE: Related Histologies  
     • OTHER APPROVED INDICATIONS  
     • NEW INDICATIONS / PILOT STUDIES |

Start Optis2: 2010  
Start Gantry-2: 2010-11

„2 plus 1“ room facility

„spot scanning for mobile tumors“ – a major emphasis
Center for Proton Radiation Therapy at PSI:

Patient-Selection: the challenge of limited capacity

Technological Innovations

New indications (mandate)

Accepted Indications (treatment mandate)
Particle therapy is an evolving modality – the limits have not been reached